

## **AMENDMENT TO THE CLAIMS**

Please amend the claims without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents, as follows.

### **In the Claims:**

1. (Previously presented) A pharmaceutical composition, comprising:
  - (i) formoterol, or a pharmaceutically acceptable hydrate thereof; and
  - (ii) a steroid anti-inflammatory agent, or a pharmaceutically acceptable salt or hydrate thereof;

in a pharmacologically suitable fluid, which is propellant-free, wherein;

the composition is an aqueous composition formulated so that it is stable during long term storage, whereby the composition has an estimated shelf-life of greater than 1 month usage time at 25 °C and greater than or equal to 1 year storage time at 5 °C;

the fluid comprises water,

the formoterol free base concentration is about 5 µg/mL to about 2 mg/mL; and

the composition is formulated at a concentration for direct administration to a human in need thereof.
2. (Cancelled)
3. (Previously presented) The pharmaceutical composition of claim 1, wherein greater than about 80% of the initial formoterol is present after 1 month usage time at 25 °C and 1 year storage time at 5 °C.
4. (Original) The pharmaceutical composition of claim 1 that has been nebulized.
5. (Currently amended) The pharmaceutical composition of claim 1, wherein the pharmacologically suitable fluid further comprises a polar solvent.
6. (Original) The pharmaceutical composition of claim 5, wherein the polar solvent is a protic solvent.

7. (Original) The pharmaceutical composition of claim 6, further comprising a tonicity adjusting agent.
8. (Original) The pharmaceutical composition of claim 7, wherein the tonicity adjusting agent is ammonium carbonate, ammonium chloride, ammonium lactate, ammonium nitrate, ammonium phosphate, ammonium sulfate, ascorbic acid, bismuth sodium tartrate, boric acid, calcium chloride, calcium disodium edetate, calcium gluconate, calcium lactate, citric acid, dextrose, diethanolamine, dimethylsulfoxide, edetate disodium, edetate trisodium monohydrate, fluorescein sodium, fructose, galactose, glycerin, lactic acid, lactose, magnesium chloride, magnesium sulfate, mannitol, polyethylene glycol, potassium acetate, potassium chlorate, potassium chloride, potassium iodide, potassium nitrate, potassium phosphate, potassium sulfate, propylene glycol, silver nitrate, sodium acetate, sodium bicarbonate, sodium biphosphate, sodium bisulfite, sodium borate, sodium bromide, sodium cacodylate, sodium carbonate, sodium chloride, sodium citrate, sodium iodide, sodium lactate, sodium metabisulfite, sodium nitrate, sodium nitrite, sodium phosphate, sodium propionate, sodium succinate, sodium sulfate, sodium sulfite, sodium tartrate, sodium thiosulfate, sorbitol, sucrose, tartaric acid, triethanolamine, urea, urethan, uridine or zinc sulfate.
9. (Original) The pharmaceutical composition of claim 8, wherein the tonicity adjusting agent is sodium chloride.
10. (Original) The pharmaceutical composition of claim 1, wherein the pharmacologically suitable fluid comprises a buffer.
11. (Previously presented) The pharmaceutical composition of claim 10, wherein the buffer is citric acid/phosphate, acetate, barbital, borate, cacodylate, citrate, collidine, formate, maleate, phosphate, succinate, citrate-phosphate-borate (Teorell-Stanhagen), veronal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane), ADA (N-(2-acetamido)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-amino-ethanesulfonic acid), PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid)), MOPS (3-(N-morpholino)-2-hydroxypropanesulfonic acid), BIS-TRIS

PROPANE (1,3-bis(tris(hydroxymethyl)methylamino)propane), BES (N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid), MOPS (3-(N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid), HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid), DIPSO (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropan- esulfonic acid), MOBS (4-(N-morpholino)butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methylamino)-2-hydroxy-propanesulfonic acid), tris(hydroxymethylaminomethane, HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxypropanesulfonicacid), POPSO (piperazine-N,N'-bis(2-hydroxypropane- sulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)piperazine-N'-(3-propanesulfonic acid), TRICINE (N-tris(hydroxymethyl)methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2-hydroxyethyl)glycine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4-butanesulfonic acid)), TAPS (N-tris(hydroxy-methyl)methyl-3-aminopropanesulfonic acid), or AMPD (2-amino-2-methyl-1,3-propanediol) buffer.

12. (Original) The pharmaceutical composition of claim 11, wherein the buffer is citrate buffer.

13. (Original) The pharmaceutical composition of claim 12, wherein the buffer concentration is from about 0.01 mM to about 150 mM.

14. (Original) The pharmaceutical composition of claim 13, wherein the buffer concentration is from about 1 mM to about 20 mM.

15. (Original) The pharmaceutical composition of claim 14, wherein the buffer concentration is about 5 mM.

16. (Original) The pharmaceutical composition of claim 8, wherein the ionic strength of the composition is about 0 to about 0.4.

17. (Original) The pharmaceutical composition of claim 16, wherein the ionic strength of the composition is about 0.05 to about 0.16.

18. (Original) The pharmaceutical composition of claim 1, wherein the pH of the composition is about 2.0 to about 8.0.
19. (Original) The pharmaceutical composition of claim 18, wherein the pH of the composition is about 4.0 to about 6.0.
20. (Original) The pharmaceutical composition of claim 19, wherein the pH of the composition is about 4.5 to about 5.5.
21. (Original) The pharmaceutical composition of claim 20, wherein the pH of the composition is about 5.0.
22. (Cancelled)
23. (Previously presented) The pharmaceutical composition of claim 1, wherein the formoterol free base concentration is about 10  $\mu\text{g}/\text{mL}$  to about 1  $\text{mg}/\text{mL}$ .
24. (Original) The pharmaceutical composition of claim 23, wherein the formoterol free base concentration is about 50  $\mu\text{g}/\text{mL}$  to about 200  $\mu\text{g}/\text{mL}$ .
25. (Original) The pharmaceutical composition of claim 24, wherein the formoterol free base concentration is about 59  $\mu\text{g}/\text{mL}$ .
26. (Original) The pharmaceutical composition of claim 24, wherein the formoterol free base concentration is about 118  $\mu\text{g}/\text{mL}$ .
27. (Original) The pharmaceutical composition of claim 8, further comprising a buffer.
28. (Previously presented) The pharmaceutical composition of claim 27, wherein the buffer is citric acid/phosphate, acetate, barbital, borate, cacodylate, citrate, collidine, formate, maleate,

phosphate, succinate, citrate-phosphate-borate (Teorell-Stanhagen), veronal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane), ADA (N-(2-acetamido)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-amino-ethanesulfonic acid), PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid)), MOPSO (3-(N-morpholino)-2-hydroxypropanesulfonic acid), BIS-TRIS PROPANE (1,3-bis(tris(hydroxymethyl)methylamino)propane), BES (N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid), MOPS (3-(N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid), HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid), DIPSO (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropanesulfonic acid), MOBS (4-(N-morpholino)butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methylamino)-2-hydroxypropanesulfonic acid), tris(hydroxymethylaminomethane), HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxypropanesulfonic acid), POPSO (piperazine-N,N'-bis(2-hydroxypropane-sulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)piperazine-N'-(3-propanesulfonic acid), TRICINE (N-tris(hydroxymethyl)methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2-hydroxyethyl)glycine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4-butanesulfonic acid)), TAPS (N-tris(hydroxy-methyl)methyl-3-aminopropanesulfonic acid), or AMPD (2-amino-2-methyl-1,3-propanediol) buffer.

29. (Original) The pharmaceutical composition of claim 28, wherein the buffer is citrate buffer.

30. (Original) The pharmaceutical composition of claim 29, wherein the buffer concentration is from about 0.01 mM to about 150 mM.

31. (Original) The pharmaceutical composition of claim 30, wherein the buffer concentration is from about 1 mM to about 20 mM.

32. (Original) The pharmaceutical composition of claim 31, wherein the buffer concentration is about 5 mM.

33. (Original) The pharmaceutical composition of claim 27, wherein the ionic strength of the composition is about 0 to about 0.4.

34. (Original) The pharmaceutical composition of claim 33, wherein the ionic strength of the composition is about 0.05 to about 0.16.

35. (Original) The pharmaceutical composition of claim 27, wherein the pH of the composition is about 2.0 to about 8.0.

36. (Original) The pharmaceutical composition of claim 35, wherein the pH of the composition is about 4.0 to about 6.0.

37. (Original) The pharmaceutical composition of claim 36, wherein the pH of the composition is about 4.5 to about 5.5.

38. (Original) The pharmaceutical composition of claim 37, wherein the pH of the composition is about 5.0.

39. (Cancelled)

40. (Previously presented) The pharmaceutical composition of claim 27, wherein the formoterol free base concentration is about 10  $\mu\text{g}/\text{mL}$  to about 1  $\text{mg}/\text{mL}$ .

41. (Original) The pharmaceutical composition of claim 40, wherein the formoterol free base concentration is about 50  $\mu\text{g}/\text{mL}$  to about 200  $\mu\text{g}/\text{mL}$ .

42. (Original) The pharmaceutical composition of claim 41, wherein the formoterol free base concentration is about 59  $\mu\text{g}/\text{mL}$ .

43. (Original) The pharmaceutical composition of claim 41, wherein the formoterol free base concentration is about 118  $\mu\text{g}/\text{mL}$ .

44. (Original) The pharmaceutical composition of claim 25 that has been nebulized.
45. (Original) The pharmaceutical composition of claim 26 that has been nebulized.
46. (Original) The pharmaceutical composition of claim 42 that has been nebulized.
47. (Original) The pharmaceutical composition of claim 43 that has been nebulized.
48. (Original) The pharmaceutical composition of claim 27 that has been nebulized.
49. (Original) The pharmaceutical composition of claim 42, wherein the buffer is citrate buffer.
50. (Original) The pharmaceutical composition of claim 42, wherein the buffer concentration is about 5 mM.
51. (Original) The pharmaceutical composition of claim 42, wherein the ionic strength of the composition is about 0.05 to about 0.16.
52. (Original) The pharmaceutical composition of claim 42, wherein the pH of the composition is about 5.0.
53. (Original) The pharmaceutical composition of claim 42, wherein the buffer is citrate buffer; the buffer concentration is about 5 mM; the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.
54. (Original) The pharmaceutical composition of claim 43, wherein the buffer is citrate buffer.
55. (Original) The pharmaceutical composition of claim 43, wherein the buffer concentration

is about 5 mM.

56. (Original) The pharmaceutical composition of claim 43, wherein the ionic strength of the composition is about 0.05 to about 0.16.

57. (Original) The pharmaceutical composition of claim 43, wherein the pH of the composition is about 5.0.

58. (Original) The pharmaceutical composition of claim 43, wherein the buffer is citrate buffer; the buffer concentration is about 5 mM; the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

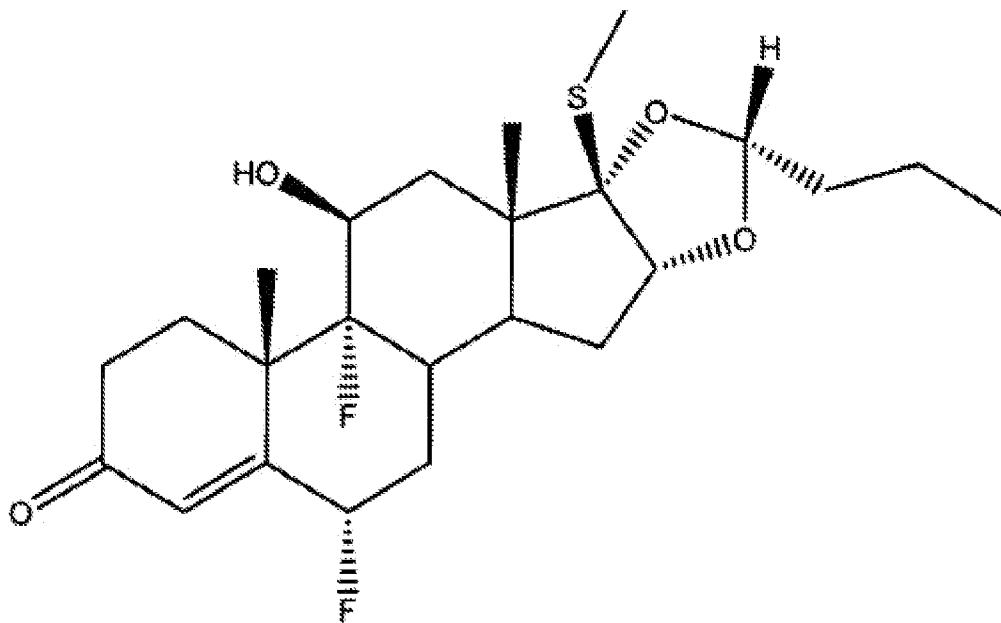
59. (Original) The pharmaceutical composition of claim 53 that has been nebulized.

60. (Original) The pharmaceutical composition of claim 58 that has been nebulized.

61. (Original) The pharmaceutical composition of claim 11, wherein the buffer comprises citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer.

62. (Original) The pharmaceutical composition of claim 27, wherein the buffer comprises citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer.

63. (Previously presented) The pharmaceutical composition of claim 1, wherein the steroid anti-inflammatory agent is beclomethasone dipropionate, beclomethasone monopropionate, flunisolide, triamcinolone acetonide, dexamethasone, tipredane, ciclesonid, rofleponide, mometasone, mometasone furoate, RPR 106541 having the formula



fluticasone or fluticasone propionate or budesonide, or a pharmaceutically acceptable salt or hydrate thereof.

64. (Previously presented) The pharmaceutical composition of claim 63, wherein the steroidal anti-inflammatory agent is budesonide or fluticasone propionate, or a pharmaceutically acceptable salt or hydrate thereof.

65. (Withdrawn) The pharmaceutical composition of claim 64, wherein the steroidal anti-inflammatory agent is budesonide, or a derivative thereof.

66. (Withdrawn) The pharmaceutical composition of claim 65, wherein the budesonide concentration is about 5  $\mu$ g/mL to about 2 mg/mL.

67. (Withdrawn) The pharmaceutical composition of claim 65, wherein the budesonide concentration is about 75  $\mu$ g/mL to about 500  $\mu$ g/mL.

68. (Withdrawn) The pharmaceutical composition of claim 65, wherein the budesonide concentration is about 125  $\mu$ g/mL or about 250  $\mu$ g/mL.

69. (Original) The pharmaceutical composition of claim 64, wherein the steroid anti-inflammatory agent is fluticasone propionate.

70. (Original) The pharmaceutical composition of claim 69, wherein the concentration of fluticasone propionate is about 5  $\mu\text{g}/\text{mL}$  to about 2 mg/mL.

71. (Original) The pharmaceutical composition of claim 70, wherein the concentration of fluticasone propionate is about 75  $\mu\text{g}/\text{mL}$  to about 1000  $\mu\text{g}/\text{mL}$ .

72. (Original) The pharmaceutical composition of claim 71, wherein the concentration of fluticasone propionate is about 125  $\mu\text{g}/\text{mL}$  or about 250  $\mu\text{g}/\text{mL}$ .

73. (Original) The pharmaceutical composition of claim 53, wherein the steroid anti-inflammatory agent is budesonide or fluticasone propionate.

74. (Original) The pharmaceutical composition of claim 58, wherein the steroid anti-inflammatory agent is budesonide or fluticasone propionate.

75. (Original) The pharmaceutical composition of claim 1 that is a solution.

76. (Original) The pharmaceutical composition of claim 1 that is a suspension.

77. (Cancelled)

78. (Previously presented) A kit, comprising:

(a) an aqueous composition comprising

- (i) formoterol or a derivative thereof, wherein the formoterol is present at a concentration of 5 $\mu\text{g}/\text{ml}$  to about 2 mg/ml; and
- (ii) a steroid anti-inflammatory agent or a pharmaceutically acceptable salt or hydrate thereof, formulated for single dosage administration, wherein the aqueous

composition is propellant-free and has an estimated shelf-life of greater than 1 month usage time at 25 °C and greater than or equal to 1 year storage time at 5 °C; and

(b) a nebulizer.

79. (Original) The kit of claim 78, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 59 µg/mL; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 5 mM; wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

80. (Original) The kit of claim 78, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 118 µg/mL; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 5 mM; wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

81. (Original) A combination, comprising:

(a) the pharmaceutical composition of claim 1 formulated for single dosage administration; and  
(b) a vial.

82. (Original) The combination of claim 81, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 59 µg/mL; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 5 mM; wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

83. (Original) The combination of claim 81, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 118 µg/mL; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 5 mM; wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about

5.0.

84-86. (Cancelled)

87. (Currently amended) An article of manufacture, comprising packaging material, an aqueous composition comprising the composition of claim 1 formulated for single dosage administration, which is useful for treatment, ~~prevention~~ or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the composition is used for treatment or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction.

88. (Currently amended) An article of manufacture, comprising packaging material, the composition of claim 73 formulated for single dosage administration, which is useful for treatment, ~~prevention~~ or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the composition is used for treatment or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction.

89. (Currently amended) An article of manufacture, comprising packaging material, the composition of claim 74 formulated for single dosage administration, which is useful for treatment, ~~prevention~~ or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the composition is used for treatment or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction.

90-92. (Cancelled)

93. (Original) The pharmaceutical composition of claim 1, further comprising one or more of (a) to (j) as follows: (a) a  $\beta$ 2-adrenoreceptor agonist; (b) a dopamine (D2) receptor agonist; (c) an IL-5 inhibitor; (d) an antisense modulator of IL-5; (e) a tryptase inhibitor; (f) a tachykinin

receptor antagonist; (g) milrinone or milrinone lactate; (h) a leukotriene receptor antagonist; (i) a 5-lipoxygenase inhibitor; or (j) an anti-IgE antibody.

94-98. (Cancelled)

99. (Original) The pharmaceutical composition of claim 13, wherein the buffer concentration is from about 1 mM to about 50 mM.

100. (Original) The pharmaceutical composition of claim 99, wherein the buffer concentration is about 20 mM.

101. (Original) The pharmaceutical composition of claim 30, wherein the buffer concentration is from about 1 mM to about 50 mM.

102. (Original) The pharmaceutical composition of claim 101, wherein the buffer concentration is about 20 mM.

103. (Original) The pharmaceutical composition of claim 42, wherein the buffer concentration is about 20 mM.

104. (Original) The pharmaceutical composition of claim 42, wherein the buffer is citrate buffer; the buffer concentration is about 20 mM; the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

105. (Original) The pharmaceutical composition of claim 43, wherein the buffer concentration is about 20 mM.

106. (Original) The pharmaceutical composition of claim 43, wherein the buffer is citrate buffer; the buffer concentration is about 20 mM; the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

107. (Original) The pharmaceutical composition of claim 104 that has been nebulized.

108. (Original) The pharmaceutical composition of claim 106 that has been nebulized.

109. (Original) The kit of claim 78, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 59  $\mu$ g/mL; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 20 mM; wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

110. (Original) The kit of claim 78, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 118  $\mu$ g/mL; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 20 mM; wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

111. (Original) The combination of claim 81, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 59  $\mu$ g/mL; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 20 mM; wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

112. (Original) The combination of claim 81, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 118  $\mu$ g/mL; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 20 mM; wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

113. (Original) The pharmaceutical composition of claim 1, further comprising an anticholinergic agent.

114. (Original) The pharmaceutical composition of claim 113, wherein the anticholinergic agent is ipratropium bromide, oxitropium bromide, atropine methyl nitrate, tiotropium bromide or glycopyrronium bromide.

115. (Original) The pharmaceutical composition of claim 114, wherein the anticholinergic agent is ipratropium bromide.

116. (Original) The pharmaceutical composition of claim 115, wherein the ipratropium bromide is present at a concentration of about 5  $\mu$ g/mL to about 5 mg/mL.

117. (Previously presented) A combination, comprising:

a composition comprising formoterol, or a pharmaceutically acceptable salt or hydrate thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, the formoterol free base concentration is about 5  $\mu$ g/mL to about 2 mg/mL, and the composition is formulated at a concentration for direct administration to a human in need thereof; and

a composition comprising a bronchodilating steroid, or a pharmaceutically acceptable salt or hydrate thereof.

118. (Original) The combination of claim 117, further comprising a nebulizer.

119. (Original) The combination of claim 118 that is packaged as a kit; optionally comprising instructions for use of the nebulizer; and optionally comprising instructions for mixing the compositions.

120. (Original) The pharmaceutical composition of claim 114, wherein the anticholinergic agent is tiotropium bromide.

121. (Original) The pharmaceutical composition of claim 115, wherein the tiotropium bromide is present at a concentration of about 5  $\mu$ g/mL to about 5 mg/mL.

122. (Previously presented) A pharmaceutical composition, comprising:

- (i) formoterol, or a pharmaceutically acceptable salt or hydrate thereof, at a concentration with reference to the free base of about 5  $\mu$ g/mL to about 2 mg/mL; and
- (ii) a steroid anti-inflammatory agent, or a pharmaceutically acceptable salt or hydrate thereof; in a pharmacologically suitable fluid, which is propellant-free, wherein:

the composition is an aqueous composition that contains buffer at a concentration of 1-20 nm, has a pH of 4 to 6, an ionic strength of 0.05-0.16, selected so that the composition has an estimated shelf-life of greater than 1 month usage time at 25 °C and greater than or equal to 1 year storage time at 5 °C.